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Original Contribution

Parity and Risk of Lung Cancer in Women

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Patterns of lung cancer incidence suggest that gender-associated factors may influence lung cancer risk. Given the association of parity with risk of some women's cancers, the authors hypothesized that childbearing history may also be associated with lung cancer. Women enrolled in the Lung Cancer Susceptibility Study at Massachusetts General Hospital (Boston, Massachusetts) between 1992 and 2004 (1,004 cases, 848 controls) were available for analysis of the association between parity and lung cancer risk. Multivariate logistic regression was used to estimate adjusted odds ratios and 95% confidence intervals. After results were controlled for age and smoking history, women with at least 1 child had 0.71 times the odds of lung cancer as women without children (odds ratio = 0.71, 95% confidence interval: 0.52, 0.97). A significant linear trend was found: Lung cancer risk decreased with increasing numbers of children ($P < 0.001$). This inverse association was stronger in never smokers ($P = 0.12$) and was limited to women over age 50 years at diagnosis ($P = 0.17$). Age at first birth was not associated with risk. The authors observed a protective association between childbearing and lung cancer, adding to existing evidence that reproductive factors may moderate lung cancer risk in women.

lung neoplasms; parity; reproduction; smoking; women

Abbreviations: CI, confidence interval; LCSS, Lung Cancer Susceptibility Study; OR, odds ratio.

Patterns of lung cancer incidence suggest that lung cancer risk may vary by gender, with women being more susceptible to the carcinogenic effects of tobacco smoke (1–4) and overrepresented among never smokers diagnosed with lung cancer (5–7). However, other investigators have not corroborated these findings (8–10). Nonetheless, lung cancer in women is also more likely than lung cancer in men to be classified as adenocarcinoma, a cell type with weaker associations with tobacco smoking (11).

These reports have led to hypotheses that reproductive events, gender-associated lifestyle factors, or hormonal exposures could explain the apparently increased susceptibility to lung cancer among females. Increasing parity is associated with reduced risks of breast and ovarian cancer (12, 13). A protective effect of parity for lung cancer has been observed in several studies (14–17), but other researchers have not corroborated this finding (18–21).

In this study, we examined the association between parity and risk of lung cancer among women in a large, ongoing, hospital-based case-control study.

MATERIALS AND METHODS

From December 1992 to December 2003, 1,004 women with lung cancer and 848 healthy female controls were accrued in the Lung Cancer Susceptibility Study (LCSS), an ongoing case-control study of lung cancer being conducted at Massachusetts General Hospital (Boston, Massachusetts) (22, 23). Eligible cases included any person aged 18 years or more with a diagnosis of histologically confirmed primary lung cancer who was evaluated by the pulmonary, thoracic surgery, or hematology-oncology unit at Massachusetts General Hospital for surgery, chemotherapy, and/or radiation treatment. Controls were first recruited among healthy friends and nonblood relatives of the cases, usually

spouses ($n = 455$). ''Case-unrelated'' controls were recruited from healthy friends and spouses of randomly selected Massachusetts General Hospital patients with other solid tumors or cardiothoracic disease ($n = 393$). The participation rate is approximately 85% of eligible cases and 80% of controls.

Data collection

At study enrollment, a modified standardized American Thoracic Society respiratory questionnaire (http://www.cdc.gov/niosh/atswww.txt) was completed for each case and control by a trained research nurse (24). The questionnaire collected information on age at initiation of smoking, average number of cigarettes smoked daily, years of smoking, and time since quitting smoking for ex-smokers. Pack-years of smoking were calculated by multiplying the mean number of packs of cigarettes smoked per day by the number of years of smoking, taking into account smoking cessation periods. Three categories of smoking status were determined: never smokers (persons who had smoked fewer than 100 cigarettes in their lifetime), former smokers (persons who had quit smoking more than 1 year previously), and current smokers (persons who were still smoking or had quit smoking less than 1 year previously). The questionnaire also included questions on age, race, ethnicity, prior medical conditions, educational level, self-reported duration and intensity of exposure to environmental tobacco smoke (home, workplace, and leisure time), and environmental and occupational exposure to asbestos.

The questionnaire used from 1992 to 2002 asked whether the subject had any biologic children (excluding any stepchildren and adoptive children) and the gender and date of birth of each child. The questionnaire used from 2002 onwards asked whether subjects had any biologic children (yes/no), but no information was collected on the number of children or age at first birth.

Statistical analysis

Descriptive characteristics were compared between cases and controls using Student's t test and Pearson's χ^2 test. Odds ratios and 95% confidence intervals were calculated using logistic regression. The primary analysis compared parous women ($\geq$1 child) with nulliparous women (1,004 cases, 848 controls). Number of children was also evaluated using indicator categories (0, 1, 2, 3, or $\geq$4 children) (672 cases, 779 controls). To test for a linear trend, we created an ordinal variable for number of children (0, 1, 2, 3, or $\geq$4 children). Age at first birth was studied using quartiles as well as categories ($<$20, 20–24, 25–29, or $\geq$30 years) constructed on the basis of studies of age at first birth and risk of hormone-dependent cancers.

Biologic relevance and statistical criteria were used to develop multivariate logistic models to adjust for possible confounders. Age (years), smoking status (current, never, or former smoker), pack-years of smoking (years), and time since smoking cessation for former smokers (years) were included in all models. Additional variables considered for inclusion were average number of cigarettes smoked per day, duration of smoking (years), race (Caucasian vs. non-Caucasian), educational level (less than high school graduation, high school graduation, some college, college graduation or higher), exposure to environmental tobacco smoke at home, at work, and during leisure time (sum of years of exposure), history of cancer in first-degree relatives (yes or no), and environmental and occupational exposure to asbestos (any history or none). None of these variables changed the main effect estimate by more than 10%, so they were not included in the final models. We excluded from the analysis 115 cases and 18 controls who were missing information on parity, but they were similar in terms of age and smoking status to persons with parity data. We used the inverse probability weighting method to handle missing data for the 5% of participants missing data on pack-years of smoking (25).

To further investigate the potential for residual or unmeasured confounding by lifestyle factors associated with parity, we conducted multivariate analyses among males enrolled in the LCSS as described above for women. Any discrepancy between effect estimates for the parity–lung cancer risk relation among women versus men could approximate the magnitude of unmeasured or residual confounding by lifestyle factors associated with risk (26). Age, smoking status, pack-years of smoking, time since smoking cessation (for former smokers), and educational level were included in multivariate models.

Based on biologic considerations, we evaluated effect modification by smoking history and age at diagnosis. A cutpoint of 50 years was chosen, since it is the mean age of menopause among US Caucasian women born in the mid-20th century (27). We tested the statistical significance of the cross-product term using likelihood ratio tests comparing the fuller multivariate model to the sparser model. Stratum-specific effect estimates were directly calculated in the full data set, to avoid assuming effect modification by other covariates that may vary across strata. To evaluate whether parity was associated with specific tumor cell types, we conducted subgroup analyses in which the case definition was restricted to include only 1) adenocarcinomas, 2) bronchoalveolar carcinomas, and 3) squamous cell carcinomas. Multivariate logistic regression was used to compare the frequency of nulliparity in cases with that in controls by histologic type.

The SAS statistical package, version 9.1 (SAS Institute Inc., Cary, North Carolina), was used in all statistical analyses. All P values are 2-sided.

RESULTS

Cases ($n = 1,004$) and controls ($n = 848$) differed in terms of several established risk factors for lung cancer, including age, educational attainment, smoking status, and amount smoked (Table 1). Case-related controls (54%) were similar to case-unrelated controls (46%) with respect to age and frequency of nulliparity but had a history of slightly heavier smoking.

Nulliparity was more common among cases than among controls. The age- and smoking-adjusted odds ratio was 0.71 (95% confidence interval (CI): 0.52, 0.97) (Table 2).

Table 1. Characteristics of Women Enrolled in the Lung Cancer Susceptibility Study, Boston, Massachusetts, 1992–2004

	Cases (n = 1,004)			Controls (n = 848)			P Value[a]
	No.	%	Median (SD)	No.	%	Median (SD)	
Age, years			66.2 (10.8)			58.4 (11.4)	<0.001
Caucasian race	973	97		824	97		0.75
Education							
Less than high school	130	15		73	9		<0.001
High school	348	40		278	33		0.003
Some college or college degree	385	45		485	58		<0.001
Missing data	141			12			
Smoking status							
Never smoker	102	10		332	39		<0.001
Current smoker	430	43		188	22		<0.001
Former smoker	472	47		328	39		<0.001
Pack-years of smoking							
Former smoker			41.7 (30.5)			16.6 (20.7)	<0.001
Current smoker			48.4 (32.5)			31.9 (25.3)	<0.001
Histologic type							
Adenocarcinoma	455	45					
Squamous-cell carcinoma	150	15					
Bronchoalveolar carcinoma	121	12					
Other	278	28					
Nulliparity	149	15		117	14		0.52

Abbreviation: SD, standard deviation.
[a] P value from a χ^2 test for categorical variables and a t test for continuous variables. All P values are 2-sided.

A significant linear trend was found for decreasing risk of lung cancer associated with increasing numbers of children ($P < 0.001$). While the risk associated with having 1 child was similar to the risk for nulliparous women, an increasingly protective effect was observed among women with 2 or 3 children (Table 2).

An analysis of the interaction between smoking status and parity in lung cancer risk suggested that the protective effect of prior childbearing was stronger among women without a history of active smoking (Table 3; P for interaction = 0.12). The protective effect of parity was also stronger among never and former smokers who had

Table 2. Estimated Risk of Lung Cancer Among Women by Parity, Lung Cancer Susceptibility Study, Boston, Massachusetts, 1992–2004

Analysis and Parity	Cases		Controls		Age-Adjusted		Multivariate-Adjusted[a]		P Value
	No.	%	No.	%	OR	95% CI	OR	95% CI	
Dichotomous analysis (n = 1,852)[b]	(n = 1,004)		(n = 848)						
0 (nulliparous)	149	15	117	14	1	Referent	1	Referent	
≥1	855	85	731	86	0.74	0.56, 0.99	0.71	0.52, 0.97	0.03
Categorical analysis (n = 1,451)[c]	(n = 672)		(n = 779)						
0 (nulliparous)	117	17	110	14	1	Referent	1	Referent	
1	85	13	84	11	0.97	0.63, 1.49	0.97	0.59, 1.60	
2	160	24	214	27	0.69	0.48, 0.98	0.75	0.50, 1.13	
3	136	20	194	25	0.56	0.39, 0.81	0.52	0.35, 0.79	
≥4	174	26	177	23	0.64	0.45, 0.92	0.57	0.38, 0.85	0.0003[d]

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Adjusted for age (years), smoking status (current, former, or never smoker), pack-years of smoking, and years since quitting smoking.
[b] Included cases and controls enrolled in the study between 1992 and 2004.
[c] Included cases and controls enrolled in the study between 1992 and 2002.
[d] P value from a test for linear trend with adjustment for age, smoking status, pack-years of smoking, and years since quitting smoking.

Table 3. Estimated Risk of Lung Cancer Among Women by Parity and Smoking History ($n = 1,852$), Lung Cancer Susceptibility Study, Boston, Massachusetts, 1992–2004[a]

Parity	Never Smokers ($n = 434$)						Ever Smokers ($n = 1,418$)					
	Cases		Controls		AOR[b]	95% CI	Cases		Controls		AOR[b]	95% CI
	No.	%	No.	%			No.	%	No.	%		
0 (nulliparous)	21	21	50	15	1	Referent	128	14	67	13	1	Referent
≥1	81	79	282	85	0.46	0.25, 0.85	774	86	449	87	0.82	0.58, 1.17

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

[a] $P = 0.12$ in a likelihood ratio test comparing the multivariate model containing an interaction term with the same model without the interaction term.

[b] Adjusted for age, smoking status, pack-years of smoking, and years since quitting smoking. Stratum-specific odds ratios were directly estimated in the full data set of 1,852 women.

stopped smoking at least 15 years previously (adjusted odds ratio (OR) = 0.55, 95% CI: 0.37, 0.82) as compared with current smokers and former smokers who had quit fewer than 15 years before the index date (adjusted OR = 0.87, 95% CI: 0.60, 1.25). The inverse association between parity and lung cancer risk was not observed in women under 50 years of age at the index date (Table 4), but this finding was not statistically significant (P for interaction = 0.17). In subgroup analyses where the case definition was limited to a particular histologic type, the associations between parity and lung cancer risk were similar regardless of cell type (for adenocarcinoma, adjusted OR = 0.67, 95% CI: 0.46, 0.97; for bronchoalveolar carcinoma, adjusted OR = 0.61, 95% CI: 0.34, 1.07; and for squamous cell carcinoma, adjusted OR = 0.69, 95% CI: 0.35, 1.39).

Men with 1 or more children did not differ from men without children in terms of their lung cancer risk (adjusted OR = 0.95, 95% CI: 0.69, 1.29). Parity was not significantly associated with risk of lung cancer among never-smoking men (adjusted OR = 0.89, 95% CI: 0.61, 1.28).

Among parous women, age at first birth was not associated with risk in either quartile analyses (data not shown) or categorical analyses (Table 5).

DISCUSSION

Our findings, from a large case-control study, indicate that having children is associated with a reduced risk of lung cancer among women. This protective effect was most pronounced among never smokers and among women older than 50 years at diagnosis. To our knowledge, this analysis is the first to have evaluated the relation between parity and lung cancer risk in men, allowing estimation of the magnitude of potential unmeasured or residual confounding by lifestyle factors associated with having children.

Investigators in several prior studies have examined the relation between parity and risk of lung cancer in populations with varying smoking and reproductive behaviors, with inconsistent results. A protective effect of parity has been observed in case-control studies conducted in the Czech Republic (15) and Germany (16), in Singapore Chinese nonsmokers (14), and in a mostly never-smoking Chinese population (17). However, a null association was reported in a predominantly (80%) Caucasian case-control study of nonsmoking women, though only 17 nulliparous cases were available (20). In a cohort study of Japanese nonsmokers, Liu et al. (18) reported no significant change in risk when comparing women with 3–4 and ≥5 children to those with 0–2 children. A nonsignificant 18% increase in risk associated with parity was found in a cohort study of 80,835 Canadian women (750 cases), along with a modest increase in risk with increasing parity (P for trend = 0.02) (19). However, both of these cohorts were younger than the LCSS population, and we did not observe an association between parity and lung cancer risk among women under age 50 years. In a case-control study (nearly 25% African-American) conducted in the Metropolitan Detroit Cancer

Table 4. Estimated Risk of Lung Cancer Among Women by Parity and Age of Onset[a] ($n = 1,852$), Lung Cancer Susceptibility Study, Boston, Massachusetts, 1992–2004[b]

Parity	Age of Onset < 50 Years ($n = 324$)						Age of Onset ≥ 50 Years ($n = 1,528$)					
	Cases		Controls		AOR[c]	95% CI	Cases		Controls		AOR[c]	95% CI
	No.	%	No.	%			No.	%	No.	%		
0 (nulliparous)	20	22	59	25	1	Referent	129	14	58	9	1	Referent
≥1	72	78	173	75	1.03	0.65, 1.63	783	86	558	91	0.65	0.47, 0.90

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

[a] For both cases and controls, age at study enrollment was used as the index date.

[b] $P = 0.17$ in a likelihood ratio test comparing the multivariate model containing an interaction term with the same model without the interaction term.

[c] Adjusted for age, smoking status, pack-years of smoking, and years since quitting smoking. Stratum-specific odds ratios were directly estimated in the full data set of 1,852 women.

Table 5. Estimated Risk of Lung Cancer Among Women by Age at First Birth[a] ($n = 1,459$), Lung Cancer Susceptibility Study, Boston, Massachusetts, 1992–2004

Age at First Birth, years	Cases ($n = 683$)		Controls ($n = 776$)		Adjusted Odds Ratio[b]	95% Confidence Interval
	No.	%	No.	%		
Nulliparous	149	22	117	15	1	Referent
<20	90	13	95	12	0.55	0.35, 0.85
20–24	268	39	303	39	0.48	0.34, 0.68
25–29	115	17	184	24	0.43	0.29, 0.64
≥30	61	9	77	10	0.60	0.36, 0.99

[a] Participants enrolled in the study between 1992 and 2002 had data collected on age at first birth.

[b] Adjusted for age, smoking status, pack-years of smoking, years since quitting smoking, and number of children.

Surveillance System, Schwartz et al. (21) found no association between number of children and lung cancer risk overall but observed a significantly increased risk among pre- or perimenopausal women (OR = 1.64, 95% CI: 1.14, 2.36). Over 14 reproductive factors were examined in relation to risk across several subgroups, raising the possibility that significant results observed were due to chance.

Biologic evidence supports a role for estrogen in lung carcinogenesis, since estrogen is involved in normal lung development (28) and in the growth and progression of non-small-cell lung cancer cells (29, 30). Estrogen can stimulate the growth of non-small-cell lung cancer cell lines in vitro (29, 30), while antiestrogenic treatments suppress tumor expansion (31). Estrogens can regulate the transcription of target genes containing estrogen-response elements in the nucleus of lung cells by interacting with estrogen receptor α or β (32, 33). Estrogen receptor transcripts and proteins, most commonly estrogen receptor β, have been isolated from tumor lung tissue and lung cancer cell lines (29, 30, 34–36). Estrogen receptor expression is evident in tumor biopsies from women and men (36–38), with 1 study reporting effect modification of the association between reproductive factors and lung cancer risk by estrogen receptor expression only among women (21).

Reproductive factors, such as nulliparity, younger age at menarche, and older age at menopause, have been associated with increased risk of hormone-dependent cancers such as breast, endometrial, and ovarian cancer. These associations may be explained by changes in systemic steroid hormone levels such as estrogen, although the precise biologic mechanism remains unclear (39–43). Reproductive factors, including use of hormone replacement therapy (16, 18, 19, 21, 44), ages at menarche and menopause (17–19, 21), and dietary phytoestrogen intake (14, 45), have also been associated with lung cancer risk.

Strengths of this study include the large number of cases and the collection of extensive information on potential confounders. Adjustment for active and passive smoking, asbestos exposure, and family history of cancer did not significantly alter the effect estimates. The sensitivity analysis conducted among males suggested that unmeasured confounding by lifestyle factors associated with childbearing may have been limited.

This study was limited by the potential for selection bias, as it was not nested within an enumerated cohort. However, control participation in the LCSS is high (77%–86% each year); participating controls represent the Massachusetts General Hospital catchment population, defined using zip code data, and are similar to the eastern Massachusetts population with respect to demographic factors and smoking behaviors measured in the Massachusetts Tobacco Survey (http://www.mass.gov/dph/mtcp). The frequency of nulliparity among study controls (14%) was also comparable to that in their birth cohorts, as reported in 20th-century parity status life tables (9%–16% for ± 1 standard deviation from the median age at enrollment) (46). It is unclear whether the 54% of controls who were spouses of male lung cancer cases were the most appropriate comparison group for female lung cancer cases, although they were comparable to case-unrelated controls with respect to age and parity. Another limitation is that the LCSS questionnaire does not collect information on number of pregnancies (including stillbirths and spontaneous or induced abortions), other reproductive factors such as age at menarche/menopause, or use of oral contraceptives or hormone replacement therapy.

In conclusion, we have shown an inverse relation between parity and risk of lung cancer, adding to existing evidence that reproductive factors are associated with lung cancer risk among women. Further studies integrating a woman's complete reproductive history with prospective biomarker studies of estrogen activity and metabolism in relation to lung cancer risk are indicated.

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